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The Role of Dendritic Signaling in the Anesthetic Suppression of Consciousness

Kaspar Meyer, M.D.

ABSTRACT

Despite considerable progress in the identification of the molecular targets of general anesthetics, it remains unclear how these drugs affect the brain at the systems level to suppress consciousness. According to recent proposals, anesthetics may achieve this feat by interfering with corticocortical top-down processes, that is, by interrupting information flow from association to early sensory cortices. Such a view entails two immediate questions. First, at which anatomical site, and by virtue of which physiological mechanism, do anesthetics interfere with top-down signals? Second, why does a breakdown of top-down signaling cause unconsciousness? While an answer to the first question can be gleaned from emerging neurophysiological evidence on dendritic signaling in cortical pyramidal neurons, a response to the second is offered by increasingly popular theoretical frameworks that place the element of prediction at the heart of conscious perception. (*ANESTHESIOLOGY* 2015; 122:1415–31)

“**H**OW do general anesthetics work?” In 2005, *Science* magazine posed this question in a special section titled “What don’t we know?,” dedicated to the greatest challenges of contemporary science.¹ “Scientists are chipping away at the drugs’ effects on individual neurons,” the article reads, “but understanding how they render us unconscious will be a tougher nut to crack.” This prediction proved correct: a decade later, we have expanded considerably our knowledge of the molecular targets of general anesthetics, but it remains enigmatic how these drugs affect the brain at the systems level. Why does the potentiation of γ -aminobutyric acid (GABA) receptors caused by propofol or desflurane cause unconsciousness? How are the brain’s computational processes affected by this and other molecular mechanisms of anesthetics, so that patients undergoing surgery cease to experience their surrounds in terms of sight, sound, and touch? Anesthesiologists and cognitive neuroscientists alike have been captivated by these questions and have proposed a number of models in an attempt to answer them, such as Flohr’s “information processing theory of anesthesia,”² Alkire’s “thalamic consciousness switch hypothesis,”^{3–6} Mashour’s “cognitive unbinding paradigm,”^{7,8} John and Pritchep’s “anesthetic cascade,”⁹ or Hudetz’s “forgotten present.”^{10,11} We shall return to some of these frameworks in a later section of the article.

One recent development is particularly intriguing. Given that the most striking feature of general anesthesia is an

interruption of the patient’s ability to perceive the environment, it would appear intuitive for anesthetics to interfere primarily with bottom-up information flow along the sensory pathways, that is, with the signals that carry perceptual information from the thalamus to the primary sensory cortices and on to unimodal and multimodal association cortices. However, the very opposite appears to be the case. Several recent studies—carried out in both humans and animals, and using a variety of different anesthetic agents—have investigated differences in directional corticocortical connectivity between the awake state and anesthesia-induced unconsciousness.^{12–21} Intriguingly, the vast majority of these studies^{12–14,16,18–21} (two exceptions^{15,17} shall be discussed later in this section) indicate that connectivity along the sensory pathways, under general anesthesia, is reduced primarily in the top-down direction. In other words, unconsciousness, which is the anesthetic endpoint this article is exclusively concerned with, appears to be correlated with reduced signaling from higher-order association cortices to early sensory cortices (table 1 and fig. 1A). It is particularly interesting to note that in humans, top-down processing appears to dominate bottom-up processing in the awake state; upon loss of consciousness, this asymmetry disappears due to a relatively selective suppression of top-down processing (fig. 1).^{13,14,18,19,21}

The results of these studies are in line with earlier electrophysiological work in animals²² and humans,²³ which demonstrated a loss of neural synchronization, under general

This article is featured in “This Month in Anesthesiology,” page 1A. Corresponding article on page 1196. All figures except figure 1B were enhanced by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

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Table 1. Recent Studies Investigating Functional Connectivity among Different Brain Areas during General Anesthesia

Study	Species	Recording Technique	Assessment Method for Directed Connectivity	Anesthetic Agent	Connectivity Changes (Increase or Decrease)
Imas <i>et al.</i> ¹²	Rats (n = 6)	Event-related potentials	Transfer entropy	Halothane Isoflurane	Frontal → Parietal Frontal → V1 Parietal → V1
Lee <i>et al.</i> ¹³	Humans (n = 10)	Baseline electroencephalography	Evolutional map approach	Propofol	Frontal → Parietal
Ku <i>et al.</i> ¹⁴	Humans (n = 18)	Baseline electroencephalography	Symbolic transfer entropy, evolutional map approach	Sevoflurane (n = 9), Propofol (n = 9)	Frontal → Parietal
Barrett <i>et al.</i> ¹⁵	Humans (n = 7)	Source-localized baseline electroencephalography	Granger causality	Propofol	Medial frontal → Medial parietal
Boly <i>et al.</i> ¹⁶	Humans (n = 8)	Source-localized baseline electroencephalography	Dynamic causal modeling	Propofol	Medial frontal → Medial parietal
Nicolaou <i>et al.</i> ¹⁷	Humans (n = 21)	Baseline electroencephalography	Granger causality	Propofol (n = 19), Sevoflurane (n = 2)	Frontal → Parietal
Jordan <i>et al.</i> ¹⁸	Humans (n = 15)	Functional magnetic resonance imaging (resting state), baseline electroencephalography	Symbolic transfer entropy, independent component analysis	Propofol	Frontal → Parietal Frontal → Occipital Frontal → Temporal (among others)
Lee <i>et al.</i> ¹⁹	Humans (n = 30)	Baseline electroencephalography	Symbolic transfer entropy	Ketamine (n = 30)	Frontal → Parietal Frontal → Temporal
Lee <i>et al.</i> ²⁰	Humans (n = 10)	Baseline electroencephalography	Directed phase lag index	Propofol	Frontal → Parietal
Blain-Moraes <i>et al.</i> ²¹	Humans (n = 28)	Baseline electroencephalography	Directed phase lag index	Ketamine	Frontal → Parietal

Note that in two cases (in the studies by Barrett *et al.*¹⁵ and Boly *et al.*¹⁶ on the one hand, and in the studies by Lee *et al.*¹⁹ and Blain-Moraes *et al.*²¹ on the other) research groups analyzed overlapping data sets using different methods of connectivity analysis.

V1 = primary visual cortex.

anesthesia, between anterior and posterior parts of the brain. The work of John *et al.*²³ is particularly noteworthy in this regard because they analyzed electroencephalography data from a total of 176 surgical patients anesthetized with a wide variety of pharmacological agents (induction of anesthesia with propofol, thiopental, or etomidate; maintenance of anesthesia with propofol, isoflurane, desflurane, or sevoflurane). As an agent-invariable effect, they found that neural activity in anterior and posterior areas of the cerebral cortex became desynchronized upon loss of consciousness and that the level of synchronization (at least as far as the frequencies in the gamma range were concerned) returned to baseline levels when consciousness was regained. Although the observation of anteroposterior uncoupling under anesthesia does not warrant any directional statements, the more recent studies discussed at the beginning of the section suggest that this finding is most likely due to a suppression of top-down signaling from anterior to posterior regions, rather than *vice versa*.

There are additional findings that suggest a preferential anesthetic effect on top-down signals. For instance, anesthesia selectively disrupts the late components of the primary visual cortex' response to flash stimuli, which are assumed to be mediated by top-down processing.²⁴ Also, anesthesia suppresses figure-ground modulation.²⁵ Figure-ground modulation refers to the observation that neurons in the primary visual cortex (V1) respond differentially to a certain stimulus depending on whether it is part of the background of an image or, alternatively, part of a circumscribed figure that "pops out."

In other words, although the visual stimulation within the limited receptive field of a V1 neuron is exactly the same in both cases, the neuron's response is modulated by surrounding context, and this modulation, which is lost under anesthesia, is assumed to be mediated by top-down signals from higher-order visual areas.^{26,27} Finally, a recent study²⁸ directly compared the influence of isoflurane anesthesia on local field potentials in the auditory cortex elicited either by bottom-up or top-down stimulation. The study comprised both *in vitro* and *in vivo* experiments (carried out in mice and rats, respectively): *in vitro*, the local field potentials were elicited by selective electrical stimulation of either bottom-up or top-down afferent fibers to the auditory cortex; *in vivo*, bottom-up stimulation consisted of simple auditory stimuli, whereas top-down stimulation consisted of visual flash stimuli that were shown to activate early auditory cortex, presumably *via* top-down projections from the secondary visual cortex. Both *in vivo* and *in vitro*, isoflurane anesthesia affected the magnitude of potentials induced through top-down pathways to a significantly higher degree than the magnitude of potentials induced through bottom-up pathways.

As mentioned at the outset of the section, two studies of directional connectivity seem to be at odds with the findings discussed so far, as they observed *increased* anteroposterior connectivity under general anesthesia.^{15,17} It is interesting to note that both of these studies, as opposed to those discussed before, used Granger causality to investigate connectivity changes, raising the question of whether methodological differences

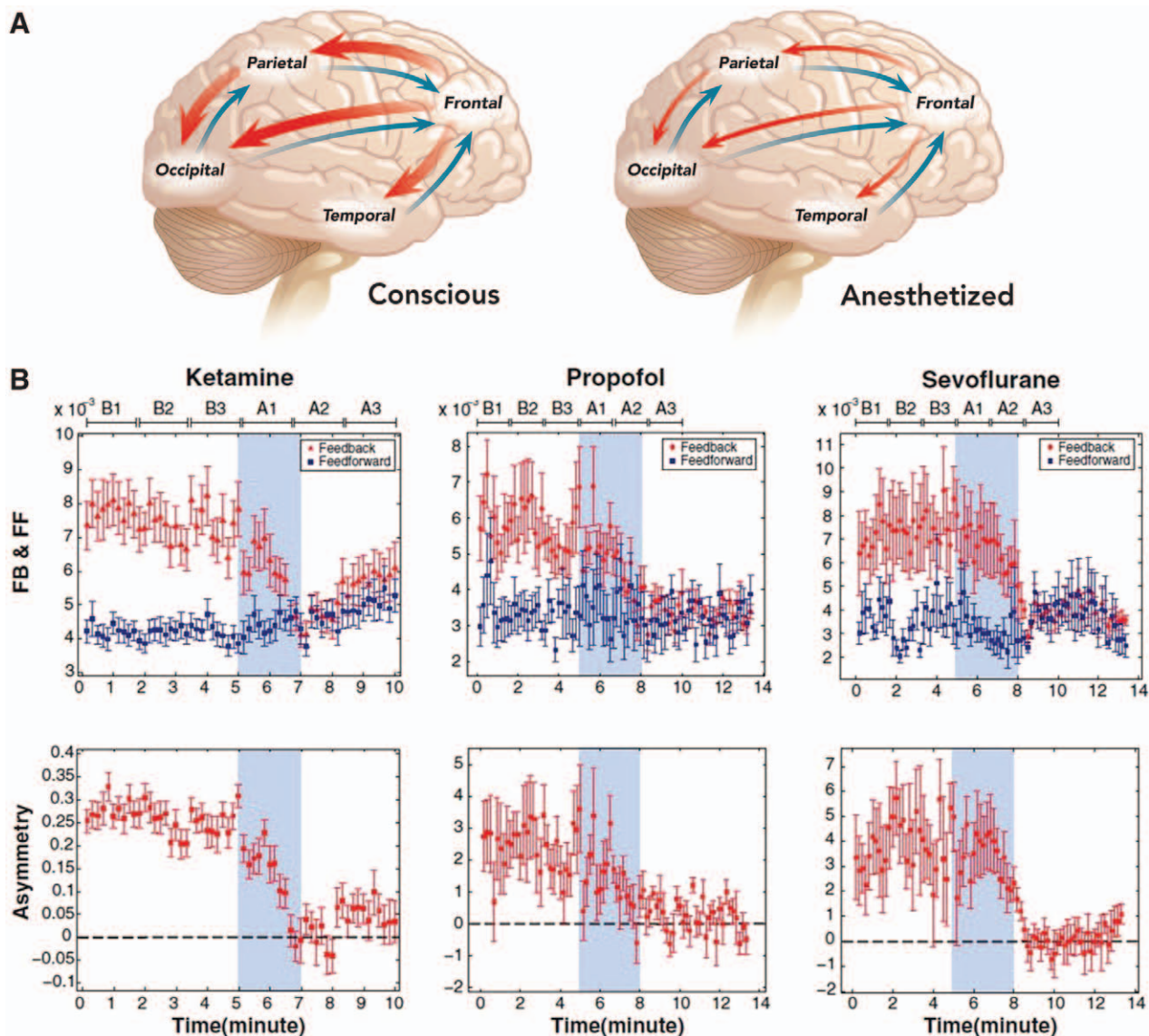


Fig. 1. Bottom-up and top-down functional connectivity in the conscious and the anesthetized brain. (A) Anesthesia affects top-down connectivity (red arrows) more significantly than bottom-up connectivity (blue arrows). Note that (1) a human brain has been chosen as figure background although some of the studies discussed in the text were carried out in animals; (2) the caliber of the arrows does not reflect study results quantitatively. (B) In human subjects, top-down connectivity (displayed in red) dominates bottom-up connectivity (displayed in blue) in the conscious state. This imbalance disappears upon loss of consciousness induced with a variety of general anesthetics due to the selective suppression of top-down signaling. The top panels display bottom-up and top-down connectivity separately, whereas the bottom panels represent subtractions of the individual data points to illustrate the imbalance between bottom-up and top-down connectivity. Note that the terms “feedback” and “feedforward” used in the figure refer to parieto-frontal and fronto-parietal connectivity, respectively, and are equivalent, in the present context, to the terms “bottom-up” and “top-down” used throughout this article. The induction phase of anesthesia is marked in light blue in all graphs. The data displayed in this figure were obtained using normalized symbolic transfer entropy; refer to table 1 for further details on the methods used in other studies. FB = feedback (top-down) connectivity; FF = feedforward (bottom-up) connectivity. Adapted, with permission, from Lee U. *Anesthesiology* 2013; 118:1264–75.¹⁹ Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

might (in part) explain the apparently contradictory findings. This conjecture is supported by the fact that one of the two studies¹⁵ represents a reanalysis of a data set for which, using a different methodology (dynamic causal modeling), a decrease in anteroposterior connectivity was demonstrated.¹⁶

To summarize, most of the data currently available suggest that general anesthesia is correlated with a decrease in top-down connectivity from frontal to parietal, temporal, and occipital cortices as well as from parietal to occipital cortices (fig. 1A). Based on these findings, Hudetz¹⁰ and

others^{5,29} have proposed that a disruption of corticocortical top-down processing may play a causal role in the anesthetic suppression of consciousness. This suggestion raises two immediate questions: First, at which anatomical site, and by virtue of which physiological mechanism, do general anesthetics interfere with top-down signaling? Second, why does a breakdown of top-down signaling cause unconsciousness?

I will now address these issues in turn. Before doing so, however, a clarifying note appears pertinent: by focusing this article on the anesthetic disruption of corticocortical top-down connectivity, I do not mean to negate the existence of other systems-level anesthetic effects or the significance of those effects for the suppression of consciousness. In other words, I do not claim that the neurobiological mechanism I introduce constitutes the common final pathway *via* which each and every anesthetic agent induces unconsciousness. To emphasize this point, the compatibility of my hypothesis with the work of others, as well as its relative relevance for different classes of anesthetics, will be discussed in separate sections toward the end of the article.

But now, let us turn to the first of the above questions: where and how do general anesthetics disrupt corticocortical top-down signals?

The Effects of General Anesthetics on Apical Dendrites of Pyramidal Neurons

Bottom-up and top-down projections along the sensory pathways follow characteristic laminar patterns of origin

and termination. While bottom-up fibers terminate predominantly in cortical layer 4 of the target area, top-down fibers target mainly layer 1,^{30–34} where they contact primarily apical dendrites of pyramidal neurons located in layers 2, 3, and 5. Traditionally, dendrites were thought to be passive conduction elements: the excitatory and inhibitory potentials induced at their synapses would be relayed to the cell soma simply *via* electrotonic spread, diminishing exponentially along the way. Because the distance between the apical synapses and the cell bodies of pyramidal neurons can be very large in cytological terms (up to 1 mm in layer 5 cells; fig. 2A), top-down signals, arriving at a very electrically remote region of their target cells, were assumed to have little influence on the firing patterns of the cells they contact. Eventually, however, it became clear that the conception of dendrites as passive conductors was incorrect, and it is now well established that there are regenerative potentials along the dendrites of several types of neurons (for a historical perspective, see the review article by Johnston and Narayanan³⁵). In cortical pyramidal neurons, for instance, a spike initiation zone capable of generating broad calcium action potentials could be identified near the main bifurcation of the apical dendrite.^{36–38} These calcium potentials carry incoming signals actively along the dendrite toward the cell body. Moreover, both *in vitro* and *in vivo* studies suggest that information impinging upon the peripheral dendritic branches is carried toward the mentioned calcium spike

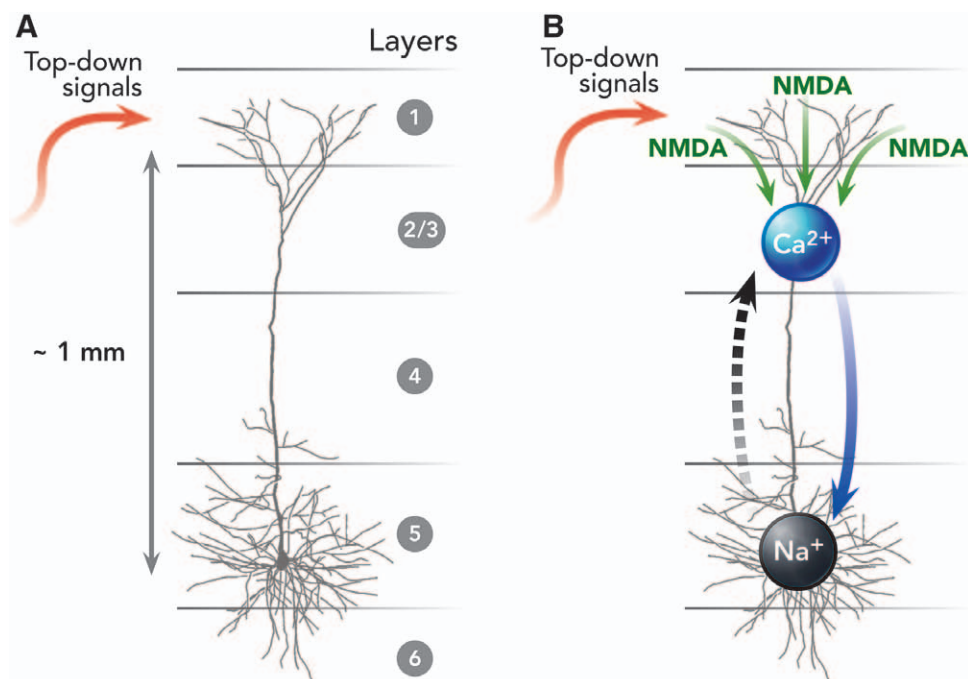


Fig. 2. Active signal conduction along the apical dendrites of layer 5 cortical pyramidal neurons. (A) Corticocortical top-down projections contact primarily distal apical dendrites, and thus a very electrically remote region, of pyramidal neurons located in deeper layers of their target area. (B) However, top-down signals impinging upon even the most peripheral tuft dendrites can be carried actively toward the cell body by means of regenerative *N*-methyl-D-aspartate (NMDA) (green arrows) and calcium (blue arrow) potentials. Of note, action potentials triggered by stimulation to the neuron's soma can back-propagate into the dendrite (black dotted arrow) and lower the threshold for dendritic calcium potentials.

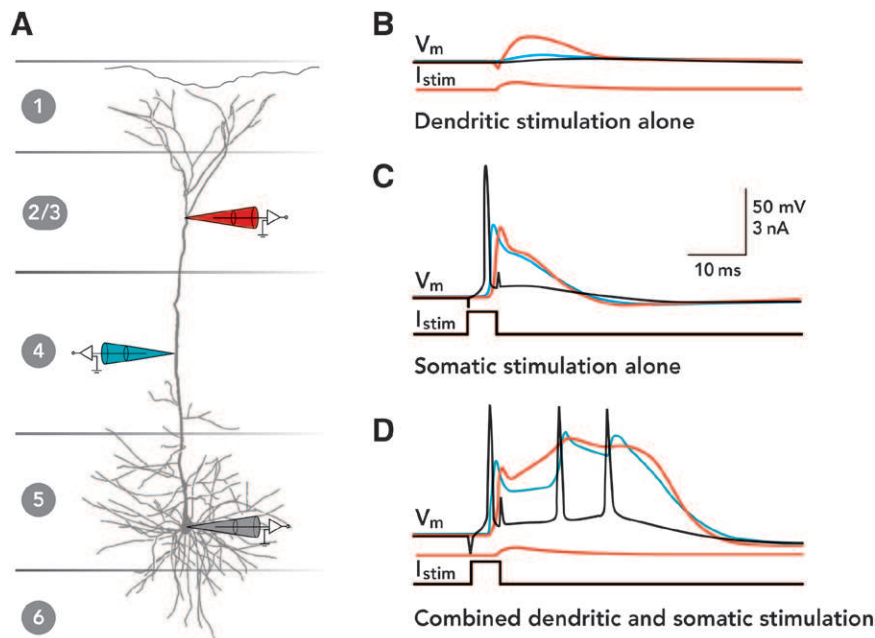


Fig. 3. Coupling of somatic and dendritic input in cortical pyramidal cells. (A) Triple recordings are made from the soma (black electrode) and two sites on the apical dendrite (blue and red electrodes) of a layer 5 pyramidal neuron. (B) Subthreshold current injection in the dendrite (red trace labeled " I_{stim} ") leads to a local depolarization of the membrane (red trace labeled " V_m "), which is, however, strongly attenuated as it migrates toward the soma (blue and black traces labeled " V_m "). (C) Threshold current injection at the soma (black trace labeled " I_{stim} ") triggers an action potential (black trace labeled " V_m ") that back-propagates into the dendrite (blue and red traces labeled " V_m "). (D) When current is injected both at the soma and in the dendrite, separated by an interval of 5 ms (red and black traces labeled " I_{stim} "), the somatic action potential (initial spike in the black trace labeled " V_m ") back-propagates into the dendrite, where it triggers a broad calcium action potential (red trace labeled " V_m "), which is carried back toward the soma, where it triggers an additional two action potentials in rapid succession (second and third spikes in black trace labeled " V_m "). Adapted, with permission, from Macmillan Publishers Ltd. and from Larkum ME. *Nature* 1999; 398:338–41.³⁸ Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

initiation zone by means of regenerative events depending on glutamate receptors of the *N*-methyl-D-aspartate (NMDA) type.^{39–42} Thus, there is an active, two-stage signaling process along the apical dendrites of pyramidal neurons: first, input to the distal tuft dendrites is carried toward the main dendrite by means of NMDA spikes; second, calcium potentials triggered close to the main bifurcation relay the signals to the soma (fig. 2B). Due to these electrogenetic mechanisms, pyramidal cells located as deep as cortical layer 5 can be exquisitely sensitive to top-down signals impinging on even the most remote tuft dendrites. In fact, triggering a calcium spike in the apical dendrite produces more output action potentials from the cell than suprathreshold input to the soma, and the action potentials occur in a characteristic high-frequency burst pattern that appears to signal specifically the presence of a dendritic calcium spike.⁴³ Of note, the two spike initiation zones (the one in the apical dendrite and the "conventional" one at the axon hillock) mutually influence one another: a single action potential triggered at the soma can back-propagate into the dendrite and lower the threshold for calcium potentials by half (figs. 2B and 3).^{38,44} Due to this mechanism, cortical pyramidal cells are in a unique position

to associate top-down signals arriving at their dendrites with bottom-up information arriving at their soma (for a review, see the article by Larkum⁴⁴), and dendritic calcium potentials, along with the subsequent characteristic action potential burst at the soma, may represent a distinctive signature of coincident somatic and dendritic activation.

Crucially, several lines of evidence suggest that general anesthetics can interfere with dendritic signal conduction and with the coupling mechanism between the dendritic and somatic action potential initiation zones in pyramidal neurons (figs. 4, A–D).

First, anesthetics have been shown to suppress the generation of dendritic calcium potentials (fig. 4A). This effect was observed both *in vitro* and *in vivo* in the barrel cortex of rats under the influence of urethane and pentobarbital.⁴⁵ Dendritic calcium activity in response to tactile stimuli was also suppressed in the primary somatosensory cortex of rats anesthetized with isoflurane; activity increased again dramatically when the animals regained consciousness, suggesting that top-down signals to the superficial cortical layers were again conducted toward the soma.⁴⁶

Second, several anesthetics are known NMDA antagonists. The most solid evidence, in this regard, has been

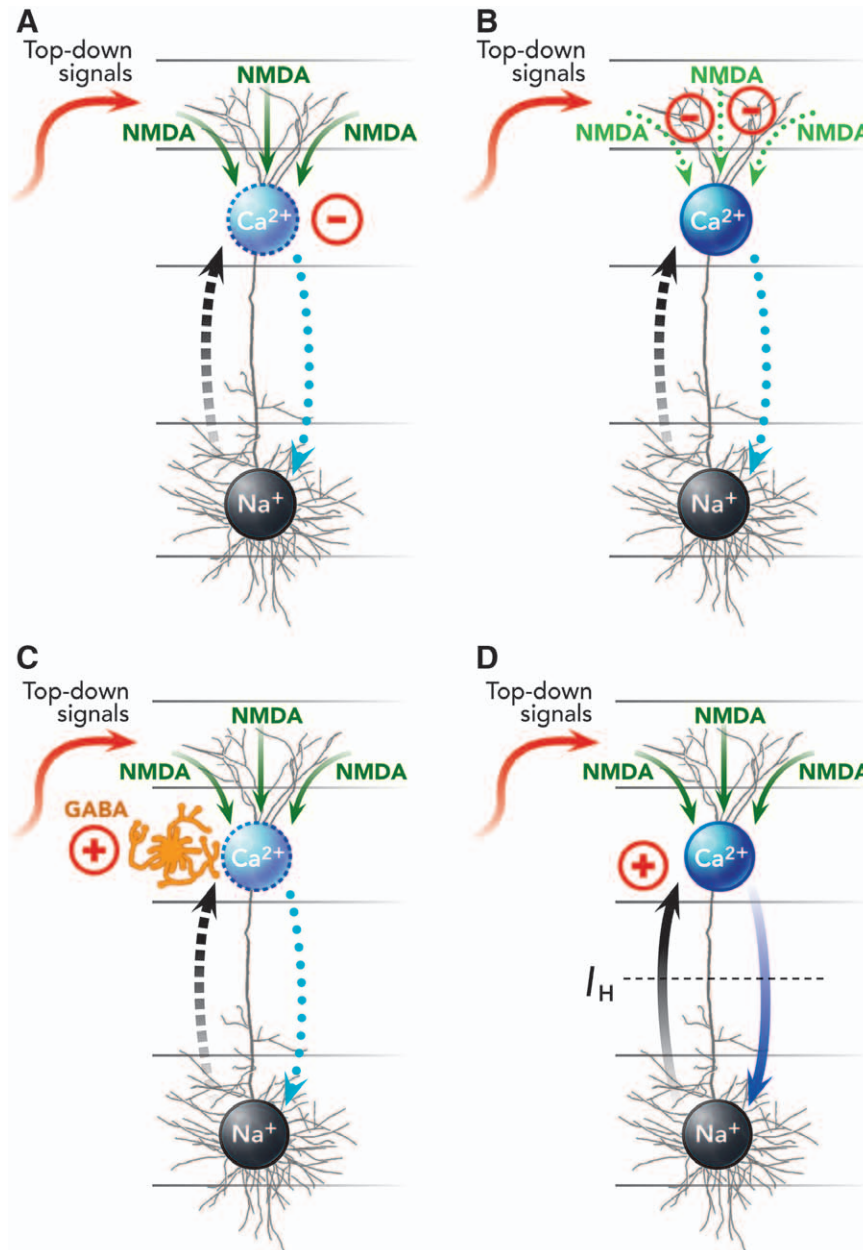


Fig. 4. General anesthetics can interfere with dendritic signal conduction in pyramidal neurons through at least four mechanisms. (A) Anesthetics can suppress the generation of dendritic calcium action potentials that carry signals along the main apical dendrite toward the soma. (B) They can suppress regenerative *N*-methyl-D-aspartate (NMDA) potentials that carry signals from peripheral tuft dendrites toward the calcium potential initiation zone. (C) Anesthetics can up-regulate inhibitory interneurons that, in turn, suppress the generation of dendritic calcium action potentials (see also fig. 5 and the accompanying legend). (D) Anesthetics can inhibit the hyperpolarization-activated current I_h , a leak conductance, which uncouples the somatic and dendritic compartments of the pyramidal cell under physiological conditions. When I_h is blocked, somatic activation alone may trigger a dendritic calcium spike and the subsequent burst of somatic action potentials, leading to a breakdown of the unique associative mechanism afforded by pyramidal cells between input to their somatic and dendritic compartments. GABA = γ -aminobutyric acid.

obtained for the dissociative anesthetic ketamine and the gaseous agents xenon and nitrous oxide, but volatile agents, such as sevoflurane and desflurane, down-regulate NMDA receptors to varying extents as well.^{47–50} Conceivably, NMDA antagonists will interfere with the generation of NMDA spikes that carry top-down signals from the peripheral tuft dendrites toward the calcium potential initiation

zone (fig. 4B). In support of this argument, a recent study showed that figure-ground modulation is suppressed by local injection of an NMDA antagonist into V1.⁵¹ Given that figure-ground modulation depends on top-down signals from higher-order visual areas,^{26,27} the authors suggested this effect may be due to a blockade of NMDA spikes in the apical pyramidal dendrites of V1 neurons. This would explain

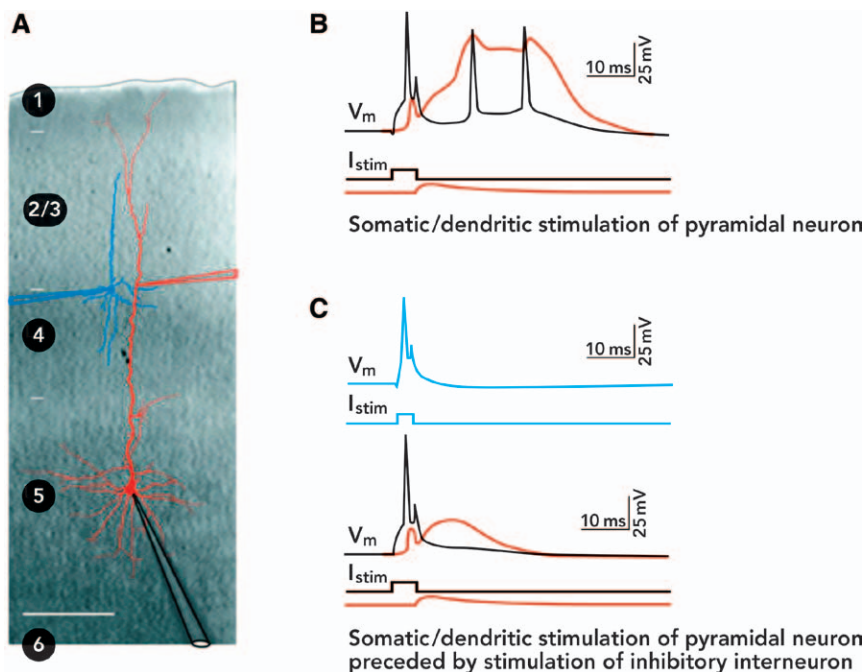


Fig. 5. Suppression of dendritic calcium potentials in pyramidal cells by inhibitory interneurons. (A) Triple recordings are made from the soma (black electrode) and the dendrite (red electrode) of a pyramidal cell, as well as from the soma of an inhibitory interneuron (blue electrode). (B) Coincident somatic and dendritic stimulation leads to a dendritic calcium potential and the characteristic burst of action potentials at the soma (similar to fig. 3D). (C) When, in parallel to the stimulation sequence displayed in B, an action potential is induced in the inhibitory interneuron (blue trace labeled " V_m "), the somatic action potential in the pyramidal neuron is still triggered (black trace labeled " V_m "), but it no longer entails a dendritic calcium spike and the subsequent burst of somatic action potentials (red and black traces labeled " V_m "). Adapted, with permission, from Macmillan Publishers Ltd. and from Larkum ME. *Nature* 1999; 398:338–41.³⁸ Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

why anesthetics with an inhibitory effect on NMDA receptors suppress figure-ground modulation, as mentioned in the preceding section.²⁵

Third, general anesthetics may interfere with dendritic signaling *via* inhibitory interneurons (fig. 4C). Pyramidal cells receive up to 80% of their inhibitory input at the dendritic arbor. Although the distance between the inhibitory synapses and the soma renders a direct influence on somatic action potential generation improbable, it has been shown that activity in inhibitory interneurons in layers 2 and 3 can suppress the initiation of dendritic calcium spikes in pyramidal neurons both *in vitro* and *in vivo*.^{38,52} This mechanism appears to be quite potent, as a single action potential in an interneuron can abolish dendritic calcium spikes in postsynaptic pyramidal cells (fig. 5).³⁸ Neuropharmacological experiments suggest that these inhibitory events rely on GABA receptors, which are a well-defined molecular target of many general anesthetics, including propofol, etomidate, barbiturates, and several volatile agents. Specifically, a short-lasting dendritic inhibition component (up to 150 ms) is mediated by GABA type A ($GABA_A$) receptors, whereas a long-lasting component (up to 400 ms) relies on GABA type B ($GABA_B$) receptors.^{52,53}

Fourth, it is interesting to note that one of the main differences between basal and apical dendrites of pyramidal

cells is the abundant presence, in the latter, of the hyperpolarization-activated current I_h .^{54,55} I_h is a leak conductance that attenuates the propagation of synaptic potentials. In cortical pyramidal neurons, I_h appears to disconnect the two spike initiation zones: under physiological conditions, although somatic action potentials lower the threshold for dendritic calcium potentials, they do not, by themselves, trigger these potentials.^{54,56} This is crucial because dendritic calcium spikes may signify specifically the simultaneous presence of somatic and dendritic activation, as mentioned at the beginning of the section. However, when I_h is blocked pharmacologically, dendritic calcium spikes can be observed in response to somatic activity alone (fig. 4D).⁵⁶ An inhibition of I_h has been observed under the influence of several volatile and intravenous anesthetics, such as halothane,^{57–59} enflurane,⁵⁷ isoflurane,⁶⁰ propofol,⁶¹ pentobarbital,⁶² and ketamine,^{63,64} indicating that all of these agents can potentially disrupt the unique associative mechanism afforded by pyramidal cells between input to their somatic and dendritic compartments.

To summarize, general anesthetics may interfere with top-down signaling at the level of the apical dendrites of cortical pyramidal neurons by virtue of at least four mechanisms or a combination thereof (fig. 4): (1) an inhibition of calcium

spike generation at the main bifurcation of the apical dendrite; (2) an inhibition of NMDA spikes in the peripheral tuft dendrites; (3) a down-regulation of dendritic signaling *via* a GABAergic enhancement of inhibitory interneurons; and (4) a down-regulation of the hyperpolarization-activated current I_h , which would interfere with the associative mechanism between bottom-up somatic and top-down dendritic input to pyramidal cells.

Top-down Signals and Conscious Perception: What We Already Know

The connectivity data presented at the outset of this article indicate that corticocortical top-down signaling is disrupted during general anesthesia, a signature state of impaired consciousness. In the light of this observation, it is intriguing to note that the interest of the cognitive neuroscience community in top-down processes—and in their significance for conscious perception, in particular—has increased enormously during the past 3 decades.

It is by now well established that there are reciprocal anatomical connections at all stages of sensory processing for at least the visual,^{30–32,65} auditory,^{33,65} and somatosensory^{34,65,66} modalities. In fact, area V1 receives top-down projections from more areas than it sends bottom-up projections to, and there appears to be a general predominance of top-down over bottom-up connectivity along the ventral visual pathway.⁶⁷

Contrary to the traditional “feedback” conception, top-down projections may drive, rather than just modulate, activity in the early sensory cortices. Mignard and Malpel⁶⁸ produced evidence to this effect more than 2 decades ago by showing that neurons in the superficial layers of V1 could be driven by signals from the secondary visual cortex (V2) after the thalamocortical projection to V1’s layer 4 had been blocked. More recent work indicates that nonstimulated regions of V1 contain information about stimuli presented elsewhere in the visual field and that they receive this information *via* corticocortical top-down (rather than lateral) projections.^{69,70} Early visual cortices also encode information about stimuli presented in modalities other than the visual,^{71,72} and analogous findings exist for the early auditory^{71,73} and somatosensory^{71,74} cortices. All of these findings indicate that top-down signals can induce, in their target areas, activity patterns of considerable resolution.

Importantly, there is substantial evidence to suggest that top-down processes not only play an important role in sensory processing in general but also are crucial for *conscious* perception, in particular^{75–82} (see also the review articles by Pollen,⁸³ Lamme and Roelfsema,⁸⁴ Bullier,⁸⁵ Hochstein and Ahissar,⁸⁶ and Meyer⁸⁷). For example, when subjects perceive apparent motion (as is the case when two dots in different locations are seen in rapid alternation, creating the impression that a single dot is moving from one location to the other), there is V1 activity along the apparent motion trace (where there is no actual visual stimulus), and this activity is induced

by top-down signals.^{82,88} Along the same lines, latency data from single-unit recordings in monkeys suggest that the perception of illusory contours (where, again, subjective experience diverges from the physical nature of the stimulus) is signaled from higher-order to lower-order visual cortices.⁷⁷ Similar findings exist for the somatosensory modality: the subjective intensity of tactile stimuli is reflected in top-down signals that reach layer 1 of the primary somatosensory cortex from higher-level areas rather than in the thalamocortical signals that initially arrive in layer 4.^{75,76} As an additional observation, which applies equally to the visual, auditory, and somatosensory modalities, there is an interdependency of the latency of sensory cortex responses and their correlation with conscious experience: although early activity in the sensory areas appears to be strictly stimulus bound, later activity, which reflects top-down signals from higher-order cortices, is correlated more closely with the subject’s conscious percept.^{24,75,76,79,89,90}

Thus, several lines of evidence from neuroanatomy, neurophysiology, and functional neuroimaging suggest that top-down signaling fulfills an indispensable function in conscious perception. Accordingly, if general anesthetics interrupt top-down processing, as suggested by the studies reviewed at the outset of the article, this would be one potential mechanism by virtue of which they may suspend consciousness. But why does an interruption of top-down signaling lead to unconsciousness, in the first place? In other words, how must we conceptualize the contribution of top-down signals to the conscious state?

Prediction as the Central Element of Conscious Perception

Several prominent scholars have proposed theoretical frameworks of consciousness that take into account the essential role of top-down processing indicated by the evidence presented in the preceding section. Most of these frameworks suggest—some implicitly, some explicitly—that the conscious mind constructs, rather than perceives, reality. Central to this idea is the element of prediction: the brain would constantly use its large repertoire of past experiences to generate the most parsimonious interpretation of the momentary sensory input constellation. An early hint at this line of thought can be found in the work of Hermann von Helmholtz⁹¹ who, almost one and a half centuries ago, in his “Handbook of Physiological Optics,” surmised that raw sensory input (“Perception”) would be modified by an expectation (“Vorstellung”) to yield the final perceptual product (“Anschauung”). More recently, Changeux and Dehaene⁹² proposed that the brain “constantly and internally [generates] varieties of hypotheses and [tests] them upon the outside world, instead of having the environment impose (instruct) solutions directly upon the internal structure of the brain.” Llinás⁹³ conceptualizes consciousness as “an intrinsic property arising from the expression of existing dispositions of the brain to be active in certain ways.

It is a close kin to dreaming, where sensory input by constraining the intrinsic functional states specifies, rather than informs, the brain of those properties of external reality that are important for survival.” Finally, according to Raichle and Mintun,⁹⁴ we should convert our “view of the brain as a system primarily responding to changing contingencies to one operating on its own, intrinsically, with sensory information interacting with rather than determining the operation of the system.” Raichle⁹⁵ based this conclusion on his quantitative studies of brain metabolism, which indicate that although the brain is an extremely active organ in metabolic terms (accounting for approximately 20% of the body’s total energy consumption while only representing approximately 2% of its weight), the additional energy burden due to the momentary demands of the environment may be as little as 0.5 to 1.0%.

Within the realm of prediction frameworks, special attention lately has been given to a model called “hierarchical predictive coding”^{96–99} (see also the recent, comprehensive review by Clark¹⁰⁰). According to this model, at each level of the sensory hierarchies predictions about the neural representations at the next lower level are generated based on previously learned associations. At the lower level, these predictions are compared with the actual sensory input, and deviations from the predictions—in other words, error signals—are returned to the higher level (fig. 6). The higher level then adjusts the original prediction and sends another version down to the lower level. Thus, to quote Clark,¹⁰⁰ hierarchical predictive coding “depicts the top–down flow as attempting to predict and fully ‘explain away’ the driving sensory signal, leaving only any residual ‘prediction errors’ to propagate information forward within the system.” (As a side note, hierarchical predictive coding can be extended to the motor domain. A comprehensive treatment of this topic is beyond the scope of the present article, but the basic idea is that sensory residual error can be minimized not only by generating updated predictions but also by adjusting body movement in a way as for the resulting sensory signals to fulfill the existing ones.^{101,102} This unifying account between perception and action is captured in Friston’s “free energy principle”).¹⁰³

In the present context, it is particularly noteworthy that, according to hierarchical predictive coding, the lion’s share of information transfer along the sensory pathways—in the form of predictions—would occur in a top–down direction, whereas bottom–up signals would merely carry residual error. To use Clark’s terms again: “...all that needs to be passed forward through the system is the error signal [...]. In these models, it is therefore the backward (recurrent) connectivity that carries the main information processing load”¹⁰⁰ (compare the number of upward arrows with the number of downward arrows in fig. 6). This conclusion is remarkably consistent with the empirical observation (as discussed at the beginning of the article) that top–down functional connectivity, at least in humans, dominates bottom–up connectivity in the awake state (fig. 1B).^{13,14,18,19,21}

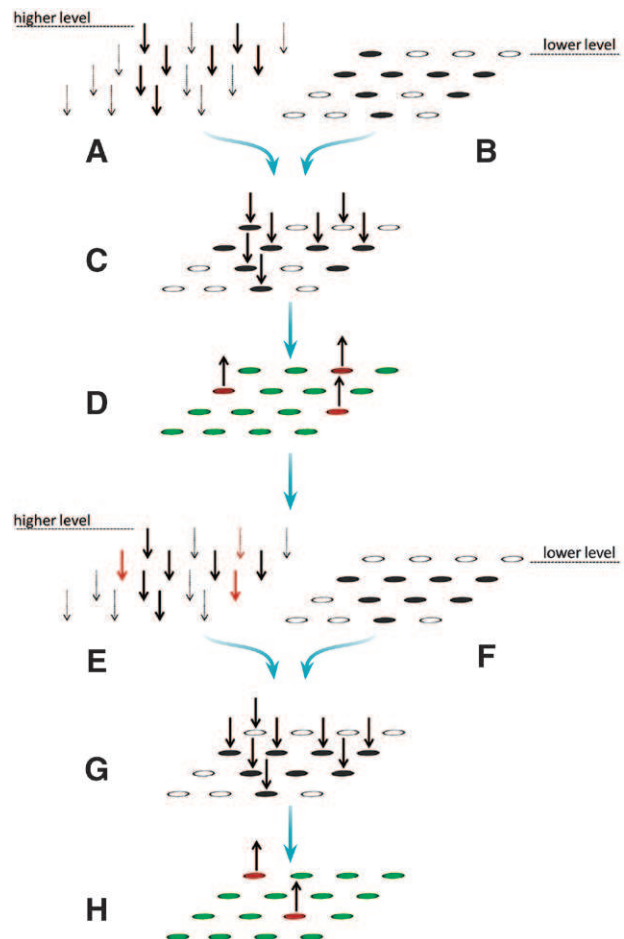


Fig. 6. Schematic representation of hierarchical predictive coding. At each level of sensory processing, predictions (A) about the activity pattern at the next lower level (B) are generated. At the lower level, the predictions are compared with the actual activity pattern (C), and error signals are returned to the higher level (D). The prediction at the higher level is adjusted (E), and a novel version is sent back to the lower level, where, meanwhile, the activity pattern may have changed (F). The updated prediction and the current pattern of activity are compared again (G), and updated error signals are returned to the higher level (H). Note that top–down information flow, according to the model, is generally greater than bottom–up information flow.

Recall that this asymmetry disappears when consciousness is lost due to a selective anesthetic suppression of top–down information flow. Thus, in terms of hierarchical predictive coding, anesthesia-induced unconsciousness would be caused by a breakdown of the top–down predictive process. While bottom–up processing would prevail, the error signals thus transmitted, in the absence of top–down predictions, would simply become meaningless. (It is interesting to note that, in an article published while the present manuscript was undergoing peer review, Raz *et al.*²⁸ suggested a similar interpretation of their finding that isoflurane anesthesia had a differential effect on bottom–up-induced and top–down-induced auditory local field potentials, as discussed toward the end of the first section of the article.)

Integrating the Present Hypothesis with Existing Frameworks of Anesthesia

Cognitive Unbinding

Several authors^{7–11}—most prominently Mashour in his “cognitive unbinding paradigm”^{7,8}—have proposed that unconsciousness may ensue when disparate brain regions become disconnected from one another: it would be the isolation, rather than the extinction, of neural activity that would cause unconsciousness.⁸ This proposal is directly related to the binding problem, one of the outstanding mysteries in cognitive neuroscience. The binding problem designates the observation that the different components making up the conscious mind are “bound together” (you see a red rose, rather than a colorless shape paired with a shapeless color) despite being encoded in spatially disparate regions of the cortex. One potential solution to this problem is the “binding by synchrony” hypothesis: neural coalitions encoding the different features of a single sensory object (such as the color and the shape of a rose) would synchronize their firing patterns, most likely in the lower gamma range around 40 Hz.^{104,105} In accordance with this proposal, early “unbinding theories” suggested that a loss of gamma coherence may be the critical factor underlying anesthesia-induced unconsciousness.^{7,9,10} This proposal received empirical support from studies (mentioned in the first section of the article) that showed a disruption of gamma synchrony between different brain areas under the influence of a wide variety of anesthetics.^{22,23} More recent work, however, has shown that gamma synchrony can persist, or even increase, under general anesthesia,¹⁰⁶ and the significance of gamma coherence for consciousness has been questioned in general.¹⁰⁷ According to a recent framework from cognitive psychology, binding would depend on top–down signals that selectively reinforce and sustain those representations in the early sensory cortices that encode aspects of sensory information that belong together.¹⁰⁸ In keeping with this development, and with the evidence implicating disrupted top–down connectivity in anesthesia-induced loss of consciousness, Mashour has reformulated his “unbinding paradigm” to move the focus away from gamma coherence toward top–down integration. In the absence of the top–down excitatory bias for the relevant neural coalitions, cognitive events would be “unbound,” and unconsciousness would ensue.⁸ Thus, Mashour’s updated “unbinding paradigm” offers an alternative explanation to predictive coding for why a breakdown of top–down signaling would lead to unconsciousness. Of note, his revised framework, due to the implication of top–down mechanisms in anesthesia-induced unconsciousness, has become more compatible with the neurobiological hypothesis presented in this article, according to which the apical dendrites of pyramidal neurons would be one of the sites of anesthetic action.

The “Thalamic Consciousness Switch”

To what extent is the present hypothesis compatible with an essential role of the thalamus in anesthesia-induced

unconsciousness? After all, neuroimaging studies suggest that a reduction of thalamic blood flow and metabolism may well be the most consistent regional effect observed under general anesthesia with a variety of agents, including propofol,^{109,110} halothane,³ isoflurane,³ and sevoflurane¹¹⁰ (see review by Alkire and Miller⁴). This has prompted Alkire and colleagues^{3–6} to propose the “thalamic consciousness switch hypothesis,” according to which a hyperpolarization block of the thalamus would prevent incoming sensory information from reaching the cortex. The evidence in support of this claim has remained controversial. For instance, because neuroimaging data correlate mostly with synaptic, rather than spiking, activity in a brain area,^{111,112} it has been argued that the decreased thalamic signal may be indicative primarily of reduced input from the brainstem or the cortex. In keeping with this view, metabolic and electrophysiological effects of anesthetics on the thalamus appear to be abolished after cortical ablation,¹¹³ and although there are instant and dramatic changes in the human cortical electroencephalogram at the onset of sevoflurane or propofol anesthesia, electrophysiological changes in the thalamus appear only later.¹¹⁴ Other findings, however, do indicate that the thalamus may be a primary site of anesthetic action. For example, a recent study carried out in rodents found that electrophysiological changes in the midline thalamus preceded those in the neocortex in the transition to both natural sleep and propofol anesthesia.¹¹⁵ This observation appears to be at odds with the data from human electroencephalography mentioned just before. In further support of the thalamus as a target of anesthetics, halothane and isoflurane have been shown to hyperpolarize thalamocortical neurons *in vitro*,^{116,117} and GABA agonists injected into the intralaminar thalamic nuclei cause a loss of the righting reflex (considered a behavioral correlate of a loss of consciousness) in rats.¹¹⁸ Moreover, Alkire’s group recently demonstrated that rats under general anesthesia can be awakened by injections of nicotine into the intralaminar nuclei¹¹⁹ or by the infusion of an antibody against a voltage-gated potassium channel in the same location.¹²⁰

A tentative interpretation of these seemingly contradictory data would be that the nonspecific thalamocortical projection, which originates in the intralaminar and midline nuclei, as opposed to the specific projection, is crucial for consciousness and its extinction during general anesthesia. Indeed, a recent functional magnetic resonance imaging study in humans investigated specifically the effect of propofol administration on functional connectivity in the nonspecific and specific thalamocortical systems and found that, under deep sedation, connectivity was reduced to a significantly greater extent in the nonspecific than in the specific system.¹²¹ Furthermore, although a decrease in thalamic metabolism may be the most consistent regional effect of general anesthetics, the cerebral cortex generally remains responsive to sensory stimulation under anesthesia^{12,24,121,122} (see the review article by Hudetz¹¹), suggesting that the metabolic suppression may

concern primarily the nonspecific thalamic nuclei, whereas the specific projections that carry perceptual information to the sensory cortices remain functional.

Of note, in the present context, whereas the specific thalamocortical fibers terminate mainly in layer 4 of their cortical target areas, the nonspecific fibers terminate primarily in superficial layer 1, which, as we have seen, is also the main afferent layer for corticocortical top-down projections. Llinás and colleagues,^{104,123,124} based on their landmark electrophysiological studies, proposed the nonspecific thalamocortical signals to play a key role in conscious perception: while the specific thalamocortical projection would carry the content of sensory signals (*e.g.*, auditory or visual information) to the cortex, the nonspecific projection would be required to conjoin these fractured perceptual components into unified cognitive events by synchronizing the individual cortical firing patterns. This conjunction process, they suggested, would be implemented by the summation of specific (to layer 4) and nonspecific (to layer 1) thalamic signals along the radial dendritic axis of cortical pyramidal neurons. In fact, they found empirical evidence for such “coincidence detection,” as they referred to it, by demonstrating supralinear summation of simultaneous thalamic input to the middle and superficial cortical layers.¹²⁵ Thus, nonspecific thalamocortical projections and corticocortical top-down projections share three intriguing characteristics: (1) based on a number of empirical observations, they both have been attributed key roles in conscious perception; (2) their connectivity is decreased under general anesthesia; and (3) they both terminate primarily in layer 1 of the sensory cortices, where the information they carry may be blocked by anesthetics interfering with dendritic signal conduction in pyramidal neurons.

The “Forgotten Present”

At the conceptual level, explaining anesthetic effects on consciousness in terms of hierarchical predictive coding creates a link to Hudetz^{10,11} “forgotten present” hypothesis, which portrays anesthesia-induced unconsciousness primarily as a consequence of an (extremely) impaired working memory. Any person, Hudetz argues, who continuously lives in the present without any reference to even the most immediate past, cannot possibly be conscious, as all cognition necessarily occurs over time. Given the well-known amnesic effects of many anesthetic agents, unconsciousness would ensue when the working memory span, under increasing doses of medication, would be reduced to a point at which even the most recent past is immediately forgotten. In analogy to Edelman’s “remembered present”¹²⁶ (see also the article by Meyer¹²⁷), which describes the ceaseless enfolded of the immediate past into the present as a prerequisite for the conscious state, Hudetz therefore conceptualizes anesthesia-induced unconsciousness as a “forgotten present.” In agreement with Hudetz’ idea, according to hierarchical predictive coding, an “isolated” consciousness of the present moment is impossible because perception is not a passive reflection of the sensory

environment at each point in time, but, instead, an active prediction/construction process of the present based on knowledge acquired in the past. Once this (re)construction process is interrupted by anesthetics, the (best interpretation of the) present can no longer be remembered, that is, is “forgotten.”

Other Models

Finally, for the sake of completeness, let it be noted that cognitive neuroscientists, over the past 2 decades, have developed a number of additional models of consciousness that emphasize the significance of top-down processes or bidirectional signaling in general. These models include Tononi’s “integrated information theory of consciousness,”¹²⁸ which has been discussed explicitly with regard to anesthesia-induced loss of consciousness,⁵ Changeux and Dehaene’s “global neuronal workspace model,”^{129,130} the principle of reentry introduced by Edelman,^{131,132} and Damasio’s framework of convergence–divergence zones.^{133,134} In principle, any of these frameworks could account for the observation that a disruption of top-down (or, more generally, bidirectional) signaling is correlated with unconsciousness although, at present, none of them appears to explain the empirical data—the dominance of top-down processing in the conscious state, in particular—quite as convincingly as the predictive coding account. A comprehensive discussion of these frameworks of consciousness—which are not necessarily mutually exclusive—is beyond the scope of the present review article, and the interested reader is directed to the referenced publications for further detail.

Relevance of the Dendritic Signaling Hypothesis for Different Classes of Anesthetics: Subcortical versus Cortical Anesthesia

As mentioned at the end of the first section of the article, the present hypothesis does not claim that an inhibition of dendritic signaling in cortical pyramidal neurons constitutes a unifying mechanism that, alone, would explain how each and every general anesthetic causes unconsciousness. While the anesthetic mechanism I propose is primarily a cortical one (“primarily” because the suppression of dendritic signal conduction will likely entail a disruption of nonspecific thalamocortical signaling as well), there are several lines of evidence to suggest that multiple classes of anesthetics act on subcortical targets as well. First, anesthesia can be performed in animals (such as tadpoles or flies) that do not have a cerebral cortex. Second, immunohistochemical studies have shown that various volatile and intravenous anesthetic agents, including halothane,¹³⁵ isoflurane,^{135,136} sevoflurane,¹³⁶ propofol,¹³⁷ pentobarbital,^{137,138} or dexmedetomidine,¹³⁹ induce changes in the expression of c-Fos (a protein commonly used as a surrogate measure of neural activity) in several brainstem and hypothalamic regions, such as the locus coeruleus,¹³⁹ the ventrolateral preoptic nucleus,^{136–139} the tuberomammillary nucleus,^{137–139}

or the orexinergic cell groups in the hypothalamus.^{136,138} Third, targeted injections of pharmacological agents into some of the anatomical structures just mentioned have been observed to change an animal's state of consciousness or to alter its susceptibility to anesthetics administered systemically. For example, injections of small quantities of pentobarbital and other GABAergic agents into the mesopontine tegmentum induce an anesthesia-like state in rats.^{140,141} Hypnosis is also caused by injection of dexmedetomidine into the locus coeruleus of rats; conversely, the hypnotic effect of intraperitoneal dexmedetomidine administration can be blocked by injection of atipamezole (a selective α_2 -adrenergic antagonist) into the same location.¹⁴² Along similar lines, sedation is caused by injection of muscimol (a GABA_A receptor agonist) into the tuberomammillary nucleus, and the effects of systemic GABAergic agents can be attenuated by injections of the GABA_A receptor antagonist gabazine into the same location.¹³⁷ (Note that because all of the anatomical structures mentioned here are believed to play an important role in the natural sleep–wake cycle, these observations have been taken to suggest that general anesthetics may act by influencing the subcortical sleep circuitry; for reviews on this topic, see, *e.g.*, the articles by Franks⁴⁸ and Franks and Zecharia¹⁴³). Finally, recovery from anesthesia induced by either propofol or dexmedetomidine is closely correlated with metabolic activations of the brainstem, hypothalamus, and thalamus.¹⁴⁴ To summarize, there is a wealth of data to suggest that several anesthetic agents—those acting on GABA receptors, in particular—exert their effects, at least in part, at the subcortical level.

In this context, it is interesting to consider the case of the dissociative agent ketamine, which has little to no effect on GABA receptors but, instead, acts mainly by inhibiting NMDA receptors and HCN1 channels which are responsible for the hyperpolarization-activated current I_h .^{49,63,64} Curiously, ketamine's effects on many brainstem and hypothalamic nuclei are quite opposite to those of the GABAergic and α_2 -adrenergic agents discussed before: it does not activate the sleep-promoting ventrolateral preoptic nucleus but, instead, promotes activity in the cholinergic, monoaminergic, and orexinergic arousal pathways.¹³⁸ Also, ketamine, as possibly the only general anesthetic, increases, rather than decreases, thalamic metabolism^{145,146} (although the referenced studies used subanesthetic doses). In the light of these pharmacological differences, it is interesting to consider the distinct clinical features of ketamine anesthesia: the patients are unresponsive to their environment but may keep their eyes open and later often recount sensory distortions and (unpleasant) hallucinations. Thus, ketamine anesthesia comes close to dissociating wakefulness from consciousness, and it is tempting to attribute this dissociation to an (almost) exclusively cortical mechanism of action, which would rely mainly on an inhibition of dendritic signaling in cortical pyramidal neurons, mediated by an antagonism of NMDA and HCN1 channels.

There are a few additional observations that are worth mentioning regarding ketamine's effects at the cortical level. For instance, it has been demonstrated that dizocilpine (also known as MK801), which, just like ketamine, inhibits NMDA receptors, has a stronger effect on inhibitory interneurons than on pyramidal cells.¹⁴⁷ In fact, due to an interneuron-mediated disinhibition of pyramidal neurons, the overall effect of dizocilpine on the latter cells is an activating one, particularly in the sensory cortices (visual, auditory, and somatosensory). This is in line with a prominent c-Fos expression observed in the visual, auditory, and somatosensory cortices upon ketamine administration.¹³⁸ Furthermore, of particular interest in the context of the dendritic signaling hypothesis, a mixture of ketamine and xylazine, as opposed to other anesthetic agents, was shown to *facilitate*, rather than inhibit, dendritic calcium potentials in pyramidal neurons in rat barrel cortex *in vitro*.⁴⁵ In terms of hierarchical predictive coding, it is tempting to speculate that the promoting action of NMDA antagonists on pyramidal neuron activity, and the facilitation of dendritic calcium spikes, in particular, would entail an aberrant increase of the top–down perceptual prediction process, which would be the physiological correlate of ketamine's psychomimetic effects.

In spite of the evidence presented in the preceding paragraph, studies of directed connectivity in humans (table 1) have indicated that ketamine does decrease top–down connectivity,^{19,21} just like several other general anesthetics. Furthermore, although ketamine promoted dendritic calcium spikes *in vitro*, as indicated earlier, it had the opposite effect (*i.e.*, an inhibition of calcium potentials) *in vivo*,⁴⁵ in accordance with the connectivity studies. Thus, data regarding ketamine's effect on corticocortical top–down signaling remain controversial, and future studies will have to yield a clearer overall picture.

As a last point on the topic, note that ketamine reproduces many of the positive and negative symptoms of schizophrenia when applied at subanesthetic doses to healthy volunteers and, therefore, has been used as a pharmacological model of psychosis. At the same time, it has been suggested that the symptoms of psychosis may be explained in terms of the predictive coding account, more specifically, in terms of an imbalance between bottom–up and top–down signaling.^{148–150} For instance, hallucinations may “involve excessively strong predictions within the hierarchical sensory cortices, conferring an apparent structure upon sensory noise such that the individual experiences a percept without sensory stimulus.”¹⁴⁹ Relating these ideas to ketamine specifically, the latter may “disturb the feedforward mechanism (prediction error signal) through AMPA up-regulation and the feedback constraint (priors) through NMDA blockade.”¹⁴⁸ Thus, “under ketamine, the subject experiences perceptual aberrations (due to AMPA up-regulation) and a reduced capacity to accommodate and ignore these aberrations (due to NMDA blockade).”¹⁴⁸ Clearly, these conjectures cannot

be directly extrapolated to the context of anesthesia due to the vastly different pharmacological doses used, but it is interesting to note, nonetheless, that the three-way relation between predictive coding, altered states of awareness, and ketamine application (or NMDA antagonism, in general) has been postulated before.

Summary and Future Directions

The purpose of the present article is two-fold. First, it aims to propose a neurobiological mechanism that could underlie the disruption of corticocortical top-down connectivity observed under the influence of a variety of general anesthetics. Second, it attempts to answer the question of why a disruption of top-down processing may lead to a suppression of consciousness. With regard to the first aim, it is hypothesized that the disruption of top-down signals occurs at the level of the apical dendrites of pyramidal neurons in the sensory cortices. With regard to the second, it is postulated that anesthesia-induced unconsciousness can be understood in terms of hierarchical predictive coding: when general anesthetics suppress top-down signaling, they disrupt the continuous evaluation process by which the brain compares its perceptual predictions with the momentary sensory input. In the absence of predictions, the bottom-up error signals, which are still generated under anesthesia, would lose their meaning.

General anesthesia involves multiple endpoints, including unconsciousness, amnesia, analgesia, and immobility, and there is a general consensus that these endpoints are mediated by different molecular mechanisms and at different anatomical locations within the central nervous system. In fact, not even the anesthetic component this article is concerned with—unconsciousness—should be assumed to be achieved *via* the same neurobiological route by all anesthetics. As speculated in the preceding section, the present proposal may be most pertinent to the actions of ketamine. Ketamine, to a first approximation, appears to dissociate wakefulness from perceptual awareness, its actions on subcortical targets involved in sleep and arousal seem to be quite contrary to those of other anesthetics, and it largely leaves vegetative function intact. In the light of these observations, one can surmise that the disruption of conscious experience induced by ketamine might be mediated first and foremost by one or several cortical mechanisms. Elucidating these mechanisms is of importance to the practice of anesthesia, as the ability to perform “cortical anesthesia,” avoiding the subcortical inhibition of vegetative function and autonomic reflexes, would promise to render anesthetic procedures much safer. Naturally, another agent that comes to mind in this context is xenon, which is assumed to act primarily as an NMDA antagonist as well^{151,152} and combines many of the properties of an ideal anesthetic, such as a low blood/gas partition coefficient, a concomitant analgesic effect, a lack of hemodynamic depression and

neurotoxicity, and no effect on atmospheric pollution.¹⁵³ So far, the clinical use of xenon has been limited by its cost, but it may become more accessible in the future. Presumably, due to its NMDA antagonism and its lacking action on (subcortical) GABA receptors, the dendritic signaling hypothesis would be of particular importance with respect to xenon, and it will be interesting to study the drug's effects on top-down connectivity in humans and dendritic signaling properties in animals.

As another topic to be addressed by future studies, it may be worthwhile to study the parallels between general anesthesia and sleep specifically from the perspective of predictive coding. Hobson and Friston^{154,155} have recently started to examine this topic and come to the remarkable conclusion that the “sleep state is one in which internal predictions are sequestered from sensory constraints. In other words, top-down predictions will fall upon deaf ears (or blind eyes) because the sensory prediction error units have been rendered insensitive [...]”¹⁵⁵ The neurophysiological specifics and evolutionary context of their hypothesis, while highly interesting, are beyond the scope of this article, but note the intriguing discrepancy between Hobson and Friston's description of natural sleep and the present characterization of anesthesia: whereas sleep, according to them, would be associated with a persistence of the (top-down) prediction process in the absence of (bottom-up) error signals, the evidence reviewed in the present article suggests a diametrically opposite understanding of anesthesia, namely, a persistence of error signals in the absence of predictions. It will be interesting to see whether this specific conceptual difference between anesthesia and sleep can be confirmed empirically by studies on directional connectivity changes in sleep.

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Competing Interests

The author declares no competing interests.

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